PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 7,816,361	)	Serial No. 10/577,470
	)	
Inventor(s): Ian Richard Matthews	)	Filed: January 11, 2007
	)	
Issue Date: October 19, 2010	)	Attorney Docket No. 006090.00023

For: IMMUNO INHIBITORY PYRAZOLONE COMPOUNDS

REQUEST FOR CERTIFICATE OF CORRECTION

U.S. Patent and Trademark Office
Customer Service Window
Randolph Building, Mail Stop: Certificate of Correction Branch
401 Dulany Street
Alexandria, VA 22314

Sir:

Pursuant to 35 U.S.C. § 254 and 37 C.F.R. § 1.322, Applicant requests the issuance of a Certificate of Correction in the above-identified patent. A copy of PTO Form 1050 is appended. The complete Certificate of Correction involves one page.

The mistakes identified in the appended Form occurred through no fault of the Applicant, as clearly disclosed by the records of the application, which matured into this patent. Enclosed for your convenience is a copy of the Amendment filed February 24, 2010.

Issuance of the Certificate of Correction containing the corrections is respectfully requested. Since these changes are necessitated through no fault of the Applicant, no fee is believed to be associated with this request. Nonetheless, should the Patent and Trademark Office determine that a fee is required, please charge our Deposit Account No. 19-0733.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Dated: June 2, 2011
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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.: 7,816,361

DATED: October 19, 2010

INVENTOR(S): Ian Richard Matthews

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 26, Claim 1, Line 23: Please delete "----NHC(=S)" and insert -- ----NHC(=O) --

Column 27, Claim 10, Line 8: Please delete "----CH_2" and insert -- ----CH_2---- --

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Electronic Acknowledgement Receipt

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Application Number:	10577470
International Application Number:	
Confirmation Number:	5057
Title of Invention:	Immuno Inhibitory Pyrazolone Compounds
First Named Inventor/Applicant Name:	Ian Richard Matthews
Customer Number:	22907
Filer:	Susan A. Wolffe/lynn hudgins
Filer Authorized By:	Susan A. Wolffe
Attorney Docket Number:	006090.00023
Receipt Date:	24-FEB-2010
Filing Date:	11-JAN-2007
Time Stamp:	10:45:41
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment Copy Claims/Response to Suggested Claims	Amdt.pdf	12264776 19d5cb4d49f9e597f4ec52c175d4974692778454	no	135

Warnings:	
Information:	

Total Files Size (in bytes):	12264776

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Confirmation No. 5057
Ian Richard Matthews	)	Group Art Unit: 1626
Serial No: 10/577,470	)	Examiner: SAEED, Kamal A.
Filed: January 11, 2007	)	Docket No. 007500.00007
For: Immuno Inhibitory Pyrazolone Compounds	)	

AMENDMENT

U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Amendment
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

In response to the Office Action mailed November 25, 2009, please amend the instant application as follows:

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this paper.

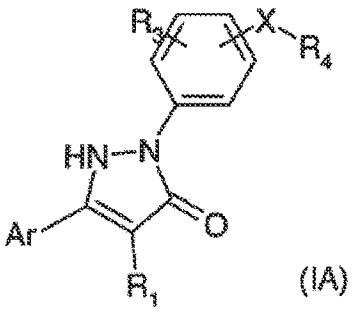
Remarks/Arguments begin on page 6 of this paper.

Please charge any fees due or credit any overpayments to Deposit Account No. 19-0733.

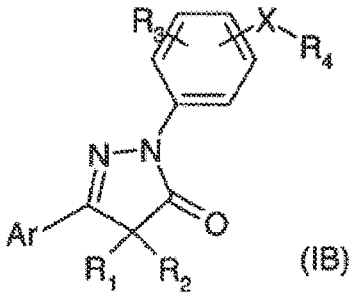
This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A compound of formula (IA) or (1B) or a pharmaceutically or veterinarily acceptable salt thereof:



(IA)



(IB)

wherein

Ar represents an optionally substituted monocyclic or bicyclic aromatic or heteroaromatic group having from 5 to 10 ring atoms,

R_1 and R_2 independently represent H, or C_1-C_6 alkyl;

R_3 represents H; F; Cl; Br; -NO_2; -CN; C_1-C_6 alkyl optionally substituted by F or Cl; or C_1-C_6 alkoxy optionally substituted by F;

R_4 represents a carboxylic acid group (-COOH) or an ester thereof, or -$C(=O)NR_6R_7$, -$NR_7C(=O)R_6$, -$NR_7C(=O)OR_6$, -NHC(=O)NR_7R_6 or -$NHC(=S)NR_7R_6$ wherein

R_6 represents H, or a radical of formula -$(Alk)_m$-Q wherein

m is 0 or 1

Alk is an optionally substituted divalent straight or branched C_1-C_{12} alkylene, or C_2-C_{12} alkenylene, or C_2-C_{12} alkynylene radical or a divalent C_3-C_{12} carbocyclic radical, any of which radicals may be interrupted by one or more -O-, -S- or -$N(R_8)$- radicals

wherein R_8 represents H or C_1-C_4 alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl, or C_3-C_6 cycloalkyl, and

Q represents H; $-CF_3$; -OH; -SH; $-NR_8R_8$ wherein R_8 is defined as above, and each R_8 may be the same or different~~, or form a ring when taken together with the nitrogen to which they are attached~~; an ester group; or an optionally substituted aryl, aryloxy, cycloalkyl, or cycloalkenyl~~ or heterocyclic group~~; and

R_7 represents H or C_1-C_6 alkyl~~; or when taken together with the atom or atoms to which they are attached R_6 and R_7 form a monocyclic heterocyclic ring having 5, 6 or 7 ring atoms~~; and

X represents a bond or a divalent radical of formula $-(Z)_n$-(Alk)- or -(Alk)-$(Z)_n$- wherein Z represents -O-, -S- or -NH-, Alk is as defined in relation to R_6 and n is 0 or 1.

2. (Original) A compound as claimed in claim 1 wherein R_1 in compounds (IA) and each of R_1 and R_2 in compounds (IB) is other than hydrogen.

3. (Previously Presented) A compound as claimed in claim 1 wherein R_4 represents a carboxylic acid group (-COOH) or an ester group of formula -COOR wherein R is methyl, ethyl n- or iso-propyl, n-, sec- or tert-butyl, or benzyl.

4. (Currently Amended) A compound as claimed in claim 1 wherein R_6 represents a radical of formula -$(Alk)_m$-Q wherein m is 1, Alk is -CH_2-, CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH(CH_3)CH_2$-, or a divalent cyclopropylene, cyclopentylene or cyclohexylene radical, optionally substituted by OH, oxo, CF_3, methoxy or ethoxy, and Q represents hydrogen; -NR_8R_8 wherein each R_8 may be the same or different and selected from hydrogen, methyl, ethyl, n- or isopropyl or tert-butyl; a methyl, ethyl or benzyl ester; or an optionally substituted phenyl, phenoxy, cyclopentyl, or cyclohexyl~~, furyl, thienyl, piperidyl, or piperazinyl~~ group.

5. (Currently Amended) A compound as claimed in claim 1 wherein R_7 represents hydrogen, methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl~~; or when taken together with the atom or atoms to which they are attached R_6 and R_7 form a monocyclic heterocyclic ring having 5, 6 or 7 ring atoms~~;.

6. (Previously Presented) A compound as claimed in claim 1 wherein Ar is optionally substituted phenyl, 2-, 3-, or 4-pyridyl, 2-, or 3-furyl, 2-, or 3-thienyl, benzfur-2-yl, or benzthien-2-yl.

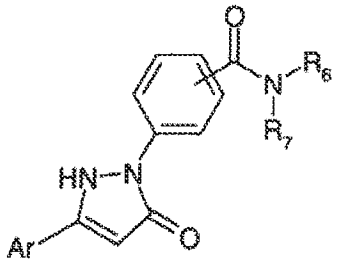
7 (Previously Presented) A compound as claimed in claim 1 wherein Ar is substituted by F, Cl, methyl, methoxy, or methylenedioxy.

8. (Previously Presented) A compound as claimed in claim 1 wherein Ar is 3-fluorophenyl, or 2- or 3-furyl.

9. (Previously Presented) A compound as claimed in claim 1 wherein R_3 is H, F, Cl, methyl, methoxy, or methylenedioxy.

10. (Previously Presented) A compound as claimed in claim 1 wherein X is a bond, or a -CH_2- or -CH_2CH_2- radical.

11. (Currently Amended) A compound as claimed in claim 1 which is of formula (IC) or a pharmaceutically or veterinarily acceptable salt thereof:



((IC)

12. (Original) A compound as claimed in claim 11 wherein the radical $-C(=O)NR_6R_7$ is in the 4-position of the phenyl ring.

13. (Previously Presented) A compound as claimed in claim 11 wherein R_7 is hydrogen and R_6 is $-AlkNR_8R_8$ wherein the R_8 groups are as defined in claim 1.

14. (Previously Presented) A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 together with a pharmaceutically or veterinarily acceptable excipient or carrier.

15. (Previously Presented) A composition according to claim 14 wherein the compound is in an amount effective for treatment of conditions which benefit from immunomodulation.

16. (Currently Amended) A medicament for the treatment of conditions which benefit from immunomodulation comprising an effective amount of the compound according to claim 1 together with a pharmaceutically or veterinarily acceptable excipient or carrier; wherein the conditions are selected from rheumatoid arthritis, psoriasis, multiple sclerosis, and diabetes.

17. (Canceled)

REMARKS/ARGUMENTS

The office action of November 25, 2009 has been carefully reviewed and these remarks are responsive thereto. Reconsideration and allowance of the instant application are respectfully requested. Claims 1-16 remain in this application. Claim 17 has been canceled without prejudice or disclaimer.

Affirmation of Restriction Requirement

Applicants confirm the election of claims 1-16. Claim 17 has accordingly been canceled. Claim 1 has also been amended in view of the elected species. The only remaining heterocyclic groups or heteroaromatic groups are those in the position of the aryl group at the 2, 5-dihydro-pyrazol moiety in the compound of formula (IA) or (IB). With respect to this aryl group, in the elected species, Ar is a 2-furyl and thus a heteroaromatic group.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 16 stands rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. This rejection is respectfully traversed.

Claim 16 has been amended to reflect that the conditions are selected from rheumatoid arthritis, psoriasis, multiple sclerosis, and diabetes. Support for these conditions is found in paragraphs 75, 71, 62, and 44 of the corresponding US published application (20070213345).

The aforementioned diseases are well-known autoimmune diseases for which treatment by the suppression of T cell activation is relevant. In T cell activation the central role is attributed to CD80/CD28 interaction. According to the data contained in the present invention the claimed compounds are qualified binders to CD80 (see table 1, in particular compounds 5, 9-15, 17-18, 26-27, 30, and 32-33, and paragraphs [0167], [0177] and [0178] of the homogenous time resolved fluorescence assay (HTRF assay). In this context, reference is made to the 2nd sentence of paragraph [0173]: "*the compounds of examples 7, 11 & 18-21 have greater affinity and longer residence times on CD80 than CD28, having K_DS of less than 100 nM, and off-rates of $2*10^{-2}$ indicating that the pyrazolones will be able to compete effectively with the endogenous ligand.*"

Therefore, the present application itself already contains convincing data that the claimed compounds are suitable for treating the autoimmune disease mentioned in amended claim 16. Furthermore, at the priority date of this application, which is November 4, 2003, it was known to the person skilled in the art that activated T cells inappropriately attack and destroy host cells of various tissues in autoimmune diseases.[1]

It was also known that T cell activation requires a co-stimulatory signal generated by the interaction of CD80 (a molecule on the surface of antigen-presenting cells) and CD28 (a molecule on the surface of T cells).[2] Therefore, at the time this application was filed, it was reasonable for one skilled in the art to consider that an agent which blocks the CD80/CD28 interaction would prevent or reduce activation of T cells, thereby reducing the damage caused by activated T cells in autoimmune diseases. In fact, many research groups have explored and continue to explore agents which act to suppress T cell activation. The relevance of suppressing T cell activation for treating autoimmune diseases is confirmed by post-filing date references, such as those provided in the IDS for rheumatoid arthritis,[3] psoriasis,[4] multiple sclerosis[5] and type 1 diabetes.[6]

Representative examples of such agents are HMG CoA reductase inhibitors[7] and tyrosine kinase inhibitors.[8] Other examples of such agents already are on the market, such as for example anti-TNF (tumor necrosis factor) antibodies which inhibit one of the major T cell pro-inflammatory cyokines. Anti-TNF antibodies include infliximab (REMICADE®), a dalimumab (D2E7/HUMIRA®) and) etanercept (ENBREL®).[9] More recently, abatacept (ORENCIA®), a protein which inhibits co-receptor signaling on T cells, has also reached the market showing good efficacy in rheumatoid arthritis.[10]

The following articles are attached to this response.

[1] see Kobata et al., *Rev. Immunogenet.* 2000, 2(1), 74-80.
[2] see Lenschow et al., *Ann. Rev. Immunol.* 1996, 14, 233-258, cited in par. 3 of the specification; see also Linsley et al. *J. Exp. Med.*, 1991, 173, 721-730; Dubey et al., *J. Immunol.*, 1995, 155, 45-47; and Suresh et al., *J. Immunol.*, 2001, 167, 5565-5573.
[3] see Cope et al., *Clin. Exp. Rheumatol.* 2007, 24, 4-11.
[4] see Choy, Curr. *Rheumatol. Rep.* 2007, 6, 437-441.
[5] see Weiss et al., *Neuroimmunol.* 2007, 191, 79-85.
[6] see Mallone and Endert, *Curr. Diab. Rep.* 2008, 8, 101-106.
[7] see Brumenau et al., *Clin. Immunol.* 2006, 119, 1-12.
[8] see Appel and Brossart, *Endocri. Metab. Immune Disord. Drug Targets,* 2007, 7, 93-97.
[9] see Kristensen et al., Scan. *J. Rheumatol.* 2007, 36, 411-417.
[10] see Chitale and Moots, *Expert. Opin. Biol. Ther.* 2008, 8, 115-122.

Claim 16 is in full compliance with the enablement requirement. Withdrawal of the present rejection is requested.

CONCLUSION

It is believed that no fee is required for this submission. If any fees are required or if an overpayment is made, the Commissioner is authorized to debit or credit our Deposit Account No. 19-0733, accordingly.

All rejections having been addressed, applicants respectfully submit that the instant application is in condition for allowance, and respectfully solicit prompt notification of the same.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Dated: February 24, 2010

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